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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

[redacted]

EXAMINER	
ART UNIT	PAPER NUMBER

05/11/01

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/983,474	Applicant(s) KLATZMAN et al
	Examiner Nirmal. S. Basi	Group Art Unit 1646

☒ Responsive to communication(s) filed on *Sep 21, 2000* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-18, 20, and 22-26* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☒ Claim(s) *1-8, 10-16, 20, 22-24, and 26* is/are allowed.

☒ Claim(s) *9, 17, 18, and 25* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Amendment filed 3/21/00 has been entered.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action (3/21/00, paper number 13).

Claim Rejection, 35 U.S.C. 112, second paragraph,

3. Claims 9 and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 is remains indefinite as it is not clear what is a CD4 derivative. Applicants arguments have been considered but not found persuasive. The term derivative encompasses modifications and mutations of the CD4. The CD4 derivative has not been defined in the specification nor claims so as to allow the metes and bounds of the claim to be determined. It is not clear what the derivative includes and excludes.

Claim 25 is indefinite as it is not clear which SEQ ID NO: amino acids 541-597 and 193-252 are referring to. The afore mentioned fragments must be refereed to by SEQ ID NO:.

Claim Rejections - 35 USC § 112, First Paragraph

4. Claim 18 remains rejected and claim 17 is under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for recombinant multimeric protein, comprising a fusion

polypeptide (linked by disulfide bridges) consisting of monomer A and monomer B of C4BP containing heterologous polypeptides in relation to the alpha and beta chains, does not reasonably provide enablement for medicaments and their uses in therapy or prophylaxis of foetomaternal alloimmunization, viral, bacterial or parasitic infections, disseminated lupus erythematosus, or other alloimmune or autoimmune diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Applicants arguments have been fully considered but not found persuasive.

The specification lists many applications which the protein of the claimed invention might or might be expected to be useful for, including: immunointervention in human immune pathologies (page 3). The specification has not taught how to treat medical conditions requiring any of the above actions. Although the specification states the object of the present invention is to achieve "immunointervention in the immune pathologies" (page 3, line 14-23), there is no disclosure of any results with the claimed fusion protein in assays, and the actual functional properties remain unknown. One skilled in the art cannot predict which fusion proteins might yield positive results. The effect of administration of the claimed fusion protein, which has no disclosed homology with other known proteins, for medical conditions is unpredictable. Furthermore, using said fusion proteins for therapy or prophylaxis would require undue experimentation.

The unpredictability in the art is shown by Haynes (Ref. A, see paper number 13). Haynes states, "major scientific obstacles blocking the development of a successful preventative HIV vaccine are the extraordinary variability of HIV, the lack of an exact animal model or HIV-induced AIDS and

the lack of understanding of the correlates of positive immunity to HIV", see abstract, page 39. Further Haynes, states that, "Current animal model of either HIV or simian immunodeficiency virus (SIV) fall short of precisely mirroring human HIV infection(10). In some such models, such as the chimpanzee, animals do not develop AIDS. Other models lack immune responses analogous to human anti-HIV T and B-cell responses. Therefore many immunotherapeutic agents would be expected to be inactive in other species. In addition, owing to the extreme complexity of the host-tumor immuno-relationship, animal models do not fully mimic the biology of human patients with cancer. Finally, the immune system is obviously different in humans and animals, and it is not surprising that immunotherapeutic agents fail to demonstrate comparable activity in animals and humans. For all these reasons it will be necessary to develop immunotherapy intended for humans in humans. Further the complexity of immune-based therapies in HIV infections and AIDS is highlighted by Fahey et al. Fahey et al disclose, "Initial therapies aiming to alter immune function in patients with HIV infection have had mixed results", see abstract. Further disclosed are that soluble CD4, CD4-IgG, immune serum/gammaglobulin, murine MoAbs to gp120 core loop have all been unsuccessful for the effective therapy for viral infections, see RECEPTOR DIRECTED TREATMENT, page 3. Some of the *in vitro-in vivo* discrepancy may be explained in part by the observation that viruses isolated from patients receiving, e.g. CD4 therapy, were 2 logs less sensitive than laboratory strains, page 3, column 1, second paragraph.. Also circulation through the liver and the kidney *in vivo* can reduce the persistence of therapeutic agents markedly, page 4, column 2, first paragraph. Further instant application claims fusion proteins, e.g containing antibodies, for treating

various diseases but has not disclosed any specific constructs that may be effective in such treatments. The epitope used to raise the antibody, nor the diseases they treat are not disclosed. Due to the large quantity of experimentation necessary to produce and isolate functional fusion polypeptides and the lack of direction/guidance presented in the specification regarding such polypeptides, the lack of working examples, the complex nature of the diseases claimed, e.g HIV infection, the unpredictability of the effects of immunotherapeutic agents in the treatment of such disease, lack of animal models, as discussed above, and the breadth of the claims which claim therapy of a spectrum of diseases without disclosure of effective chimeric polypeptides for their successful treatment, undue experimentation would be required of the skilled artisan to make and /or use the claimed invention in its full scope.

5. Claim 9 remains rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recombinant multimeric protein comprising CD4, does not reasonably provide enablement for derivative of CD4. The, specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants arguments have been fully considered but not found persuasive. While the person of ordinary skill in the art would, in light of the specification be able to make recombinant multimeric proteins comprising fusions with CD4, the scope of the claims, which encompass other fusion proteins comprising derivatives of CD4 without specific activity are not enabled by the disclosure. The disclosure does not teach how to make and purify such fusion derivatives, teach which

alterations to CD4 would result in functional fusion derivatives, or to use a commensurate number of said fusion derivatives without functional activity. Further the disclosure does not disclose the structural limitations required to produce truncated fusion polypeptides of said derivatives. Instant specification does not teach which particular amino acids are critical for the active derivative. In other words, such structurally deficient derivatives containing random mutations would be expected by the skilled artisan to result in inactive proteins. For example, Rudinger (Ref C, see paper number 13) states on page 3 that "it is impossible to attach a unique significance to any residue in a sequence. A given amino acid will not by any means have the same significance in different peptide sequences, or even in different positions of the same sequence". Rudinger further states on page 6 that "the significance of particular amino acid sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study". Therefore, the lack of guidance provided in the specification as to what minimal structural requirements are necessary for functional derivative, would prevent the skilled artisan from determining whether any modification or mutation to the CD4 molecule could be made which retains the desired function of the instant invention, because any random mutation or modification manifested within said protein itself would be predicted to adversely alter its biologically active 3-dimensional conformation, without undue experimentation to determine otherwise. Due to the large quantity of experimentation necessary to identify and purify active derivatives, the lack of direction/guidance presented in the specification regarding the identification, purification, isolation and characterization of said derivatives, the unpredictability of the effects of mutation on the structure and function of

CD4 derivatives, disclosure on how to use a commensurate number of derivatives lacking functional activity and the breadth of the claim which fail to recite functional limitations, undue experimentation would be required of the skilled artisan to make or use the claimed invention in its full scope.

6. Claims rejected 9, 17, 18 and 25

7. Claims 1-8, 10-16, 22-24 and 26 allowable.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nirmal Basi whose telephone number is (703) 308-9435. The examiner can normally be reached on Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for this Group is (703) 308-0294.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Nirmal S. Basi
Art Unit 1646
December 18, 2000

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600